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Diana DeLeo

H15 DM 10/23/86

IN THE UNITED STATES PATENT AND TRADEMARK

Applicant : Vemuri B. Reddy et al. Art Unit 127
Serial No.: 548,228 Examiner Giesser
Filed : November 2, 1983
For : HETEROPOLYMERIC PROTEINS

Commissioner of Patents and Trademarks
Washington, DC 20231

Considered JAH 1/4/87

DECLARATION OF JOHN G. PIERCE
UNDER 37 C.F.R. §1.132

Sir:

I declare:

1. I am the past Chairman of the Department of ~~Biochemistry~~ Biological Chemistry at the University of California, Los Angeles, Medical School, and I am co-author of the paper "Glycoprotein Hormones: Structure and Function" (1981) Annual Rev. Biochem. 50, 465-95, which paper is cited in an Office Action dated April 10, 1986. I have read the Office Action and the above-captioned patent application to which it refers.

2. It is my opinion that the subject matter claimed in the above-captioned patent application would not have been obvious in view of my paper and the other cited references at the time the underlying work was carried out, for the following reasons.

My paper, at pages 487-488, does, as the Office Action notes, say that "the alpha and beta subunits [of LH]

are known to associate in vitro." It is also true, as the Office Action notes, that the 1980 Fiddes et al. paper teaches the cloning of the α-hCG subunit, and that the amino acid sequence of the β-subunit of LH was known. None of these facts, however, in any way renders obvious the discovery that both subunits could be synthesized and made to associate to form an active hormone in a cell not specialized to make the hormone.

The in vitro association work mentioned in my paper has been carried out by several groups, and in each instance involved obtaining naturally occurring dimeric hormone which had been synthesized by the specialized cells which had evolved to make it, treating the hormone to cause dissociation using, e.g., urea, and then allowing the units to reassociate. Thus, the subunits which reassociated had already been synthesized in the cells naturally making them, and had been properly glycosylated and folded for reassociation prior to the experiment. This work in no way suggested that the two subunits, when synthesized by non-specialized cells transformed with recombinant DNA, would be properly glycosylated and folded for reassociation. For example, as described in Lustbader et al. (attached hereto and marked Exhibit A), the synthesis of the α-subunit by a recombinant cell, in the absence of β-subunit, yields α-subunit which contains extra carbohydrate which renders the α-subunit incapable of recombining with β-subunit.

In summary, it is my opinion that the work described and claimed in the above-captioned patent application was

895

not obvious from the references cited, or from any other references of which I am aware.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

John G. Pierce

Date: Sept 24, 1986

JGP.